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PA - (NIOF) NIPPON OILS & FATS CO LTD  
- (SANW) SANWA KAGAKU KENKYUSHO CO  
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A61K-047/24 ; A61K-047/42  
AB - J03297364 Antithrombogenic powder compsns. comprise (A) fats and oils  
contg. at least 10 wt.% of eicosapentaenoic acid and docosahexaenoic  
acid and/or fats and oils contg. 20-70 w.% of alpha-linolenic acid,  
(B) 2-20 w.% of lecithin, and (C) 20-70wt.% of protein and/or its  
hydrolysate.  
- USE/ADVANTAGE - The compsns. are pharmaceutically useful for  
prevention and treatment of arteriosclerosis such as cerebral infarct,  
myocardial infarction, and angina pectoris. They are stable for a long  
period and easy to feed. The fats and oils are derived from sardine  
(Sedum iwarenge), herrings, mackerels (Scombrina), etc., and those of  
the latter fats and oils are derived from Perilla frutescens crispa.  
The lecithin may be a mixt. of phosphatidylcholine and phospholipids,  
and is derived from soybean, egg, seed of Helianthus annuus, etc. (8pp  
Dwg.No.0/0  
CN - R00206-M R01833-M R04470-M R04471-M  
IW - ANTITHROMBOTIC POWDER COMPOSITION STABILISED COMPRISE FAT OIL CONTAIN  
EICOSA PENTENOIC ACID DOCOSA HEXENOIC ACID ALPHA LINOLENIC ACID  
IKW - ANTITHROMBOTIC POWDER COMPOSITION STABILISED COMPRISE FAT OIL CONTAIN  
EICOSA PENTENOIC ACID DOCOSA HEXENOIC ACID ALPHA LINOLENIC ACID  
NC - 001



[File name] SPECIFICATION

[Title of Invention] POWDERED COMPOSITIONS FOR PREVENTION OF  
THROMBUS

[Detailed Description of the Invention]

[Industrial field of Application]

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The present invention relates to powdered compositions for prevention of thrombus, and more particularly relates to powdered compositions for prevention of thrombus with excellent stability for a long term storage, which are useful for patients with previous history of brain infraction, cardiac infraction and/or angina, individuals with arteriosclerotic tendency and individuals with high levels of triglyceride and cholesterol in blood.

[Prior Art]

Recently, in connection with exponential growth of aged population in population structure, rapid increases of adult diseases especially such as hypertension, cardiac infraction, arteriosclerosis, thrombosis and the like have become major concerns in Japan.

Since in 1970s it was reported that adult diseases with arteriosclerosis were scarce in the regions where high levels of fish intake were observed by the epidemiological study on Inuit population in Greenland (The Lancet July, Vol. 15:117-119, 1987), importance of eicosapentaenoic acid (EPA) and docosaheptaenoic acid (DHA) has been noticed as those having

preventive effects for said diseases.

However, there are problems in which eicosapentaenoic acid and docosahexaenoic acid are readily to be oxidized due to highly unsaturated fatty acids and have a bad smell which can not eaten as foods just as it is. Therefore, fats and oils containing them are commercially available as food products, for example by coating with gelatinized capsules.

On the other hand, recently, various products obtained by spray-drying as forms of use by simply dissolving in water (Japanese Patent Laid-Open No. 60-49097, Japanese Patent Laid-Open No. 62-126933) have been considered, and the oil in water type of emulsions of purified fish oils with aqueous solutions of hydrated proteins (Japanese Patent Laid-Open No. 60-102168) have been also studied. On the one hand, fats and oils comprising lecithin and containing eicosapentaenoic acid and docosahexaenoic acid as compositions having high anti-thrombotic and anti-arteriosclerotic activity (Japanese Patent Laid-Open No. 61-112020) have been considered.

By the way, eicosapentaenoic acid and docosahexaenoic acid reveal prevention of hypertension and brain thrombus in view of the facts that they are starting fatty acids of prostaglandin E<sub>3</sub> system and have antagonistic actions of arachidonic acid metabolism.

Generally, highly unsaturated fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid have weak

points in which they are liable to undergo degradation by heat and oxygen and are unstable in storage in which nasty smell and coloring are liable to occur. And it is known that peroxides generated by oxidation of these fatty acids are harmful for human body.

Currently commercially available fish oils and capsules of concentrated eicosapentaenoic acid and docosahexaenoic acid are hard to be used by easily dissolving in water, and further belching after drinking has become a matter. Besides, currently commercially available powder products obtained by spray-drying have also a strong bad smell when drunk by dissolving in water, and further it is hard to swallow down continuously as it is, due to their bad aftertaste, and when they are combined with various foods as food materials, a fishy taste specific for fish oils spreads over inside mouth and it is liable to lose moods to have a meal. In particular, when powder products of fats and oils comprising eicosapentaenoic acid and docosahexaenoic acid are stored for two months or more after the production, a problem occurs which they are hard to be eaten because a smell of fish oils is strongly felt.

Moreover, although use of those containing eicosapentaenoic acid and docosahexaenoic acid as fats and oils has been studied, it does not appear that efficient effects are exerted for prevention of recurrence, pathological improvement and arterial sclerosis in patients with

cerebrovascular disorders. It is an actual state that no product has been ever found which possesses prevention of these symptoms, pathological improvement and sufficient furnishing of nutrition at the same time.

[Problems that the Invention is to Solve]

In this context, the present invention was conducted intending to provide the compositions having simple using forms, with excellent stability in storage, and having effects on prevention and cure of pathological improvement, arterial sclerosis and thrombosis in patients with cerebrovascular disorders, and further having sufficient furnishing of nutrition and its improvement effects.

[Means for Solving the Problems]

Having conducted intensive study to develop the compositions having said preferred nature, consequently, the present inventors have found that the objectives can be accomplished by a powdered composition containing at a specified ratio fats and oils containing a specified quantity of eicosapentaenoic acid and docosahexaenoic acid and/or fats and oils containing a specified quantity of  $\alpha$ -linolenic acid, lecithin and protein and/or its degradation matter, and then the present invention has been completed on the basis of these findings.

More specifically, the present invention is those providing a powdered composition for prevention of thrombus

characterized by containing (A) fats and oils containing 10% or more of eicosapentaenoic acid and docosahexaenoic acid by weight and/or fats and oils containing 20 % or more of  $\alpha$ -linolenic acid by weight, (B) from 2 to 20 % lecithin by weight, and (C) from 20 to 70 % protein and/or its degradation matter by weight.

The present invention is described in detail below.

In the composition of the present invention, fats and oils containing 10% or more of eicosapentaenoic acid and docosahexaenoic acid by weight, or fats and oils containing 20 % or more of  $\alpha$ -linolenic acid by weight, or mixtures thereof are used as (A) component.

As said fats and oils containing 10% or more of eicosapentaenoic acid and docosahexaenoic acid by weight, for example, table fish oils, e.g., those in which fish oils such as sardine oil, mackerel oil, herring oil, cod-liver oil and like are purified and concentrated can be used, and those extracted from bacteria and chlorella can be also used.

On the other hand, as fats and oils containing 20 % or more of  $\alpha$ -linolenic acid by weight, for example, oil of beefsteak plant seed obtained from seeds of labiate and oil from *Perilla ocimoides* are used. It is known that this  $\alpha$ -linolenic acid as well as said eicosapentaenoic acid and docosahexaenoic acid is an  $\omega$ 3 highly unsaturated fatty acid, and has preventive effects for hypertension, brain infraction

and cardiac infraction.

In the composition of the present invention, lecithin used as (B) component chemically means phosphatidyl choline, but herein refers to the mixtures with phospholipid such as phosphatidyl ethanol amine and phosphatidyl inositol. This lecithin can be prepared by extracting from, for example, soy beans, sunflower seeds, eggs and various bacteria, and can be prepared by synthesis, but use of commercially available phospholipids from soy beans or egg yolks is preferable on a cost basis. Or water-soluble lecithin treated with degreasing and enzymes can be used. In present invention, those comprising more phosphatidyl choline are suitable in the light of potentially preventing generation of a degradative smell.

In the composition of the present invention, proteins and/or their degradation matters used as (C) component include those which are nutritious proteins, have coating effects of fats and oils and have anti-oxidant action of fats and oils and lowering action of cholesterol. These can include, for example, egg proteins, whey (whey and lactalbumin) proteins, soy bean proteins, fish proteins, casein, gelatin and degradation matters thereof. These may be used alone or by combining two or more.

It is believed that these proteins are importantly involved in cholesterol metabolism and have effects to facilitate preventive and improving effects of

eicosapentaenoic acid and docosahexaenoic acid for arteriosclerosis and thrombosis. Also, protein is an important nutritional element which become component substances of body and has effects for enhancement of physical capacity and prevention of complications.

In the composition of the present invention, containing from 20 to 70 % of fats and oils containing 10 % or more of eicosapentaenoic acid and docosahexaenoic acid and/or fats and oils containing 20 % or more of  $\alpha$ -linolenic acid by weight as (A) component, from 2 to 20 % of lecithin by weight as (B) component and from 20 to 70 % of proteins and/or their degradation matters by weight as (C) component are required. If a percentage of each component deviates from said ranges, the effects of the present invention is not sufficiently exerted. Carbohydrates such as dextrin, lactose, sucrose, glucose and the like and trace nutritional elements such as vitamins, minerals and the like may be combined as needed in the composition of the present invention, and further anti-oxidant agents, emulsifiers, emulsion stabilizers, fruit juices, fragrances and the like can be added.

The emulsion stabilizers are appropriately added to make more fine oil particles and prepare for sufficiently coated states of particle peripheries with water-soluble components in preparation of a emulsified solution before disintegration, and further to well retain emulsion stability of the obtained



powdered granulated composition after dissolution. As emulsifiers, for example, sucrose fatty acid ester, fatty acid monoglyceride, propylene glycol fatty acid ester, sorbitan fatty acid ester and the like can be used, and in particular, organic acid monoglycerides such as succinate monoglyceride, citrate monoglyceride, and polyglycerine fatty acid esters such as tetraglycerine pentaoleate are suitable.

Then, describing one example of a suitable method for production of the powdered composition for prevention of thrombus of the present invention, first of all, lecithin, as well as oxidation inhibitor, emulsifier fragrance and the like used as desired are added to fats and oils, and dissolved with heating to prepare an oil phase portion. On the other hand, aside from this, at the specified ratio, proteins and/or their degradation matters, as well as carbohydrates, minerals, emulsion stabilizer, fruit juice, fragrance and the like used as needed are added to water at from 2 to 5 folds of total solid weight, and dissolved completely with stirring at from about 40 to about 80°C to prepare a water phase portion. Then, after a preliminary emulsified solution is made by mixing these water and oil phase portions with stirring, the powdered composition is produced by spray-drying. If necessary, proteins, carbohydrates, vitamins, minerals and the like may be further mixed in fine particles to this powdered composition, and then granulated using a proper granulation method. As the

granulation method, for example, a granulation method with fluidized bed manner can be used.

The powdered composition obtained in this way is good in storage stability. It is believed that storage stability becomes good because the fats and oils including eicosapentaenoic acid and docosahexaenoic acid are sufficiently protected by coating the surfaces of oil particles including eicosapentaenoic acid and docosahexaenoic acid with lecithin and by further coating their outsides with proteins. In particular, it is believed that the coating effect by lecithin is great.

The powdered composition of the present invention has functions to facilitate preventive and improving effects of thrombosis by effects of enhancement of physical capacity due to excellent storage stability and containing high quality proteins which are important nutrient elements.

In order to stably preserve this powdered composition for prevention of thrombus for a long time, tightly sealing each of from 5 to 100 g using a packing vessel with little oxygen permeability and/or a deoxidizer is desired.

The composition of the present invention, for example, may be drunk as beverages by dissolving in water or hot water, administered orally or enterally by adding to concentrated liquid foods, and further can be utilized for processed foods as food materials as it is or by dissolving.

[Examples]

The present invention is then described further in detail by the examples, but the invention is not limited to these examples.

(Example 1)

The materials at 100 parts by weight of the mixed composition shown in Table 1 were added to water at 200 parts by weight and heated up to 70°C. Soy bean lecithin and succinate monoglyceride were added after they were previously dissolved in the combined oil of the concentrated fish oil containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (EPA: 17 wt %, DHA: 12 wt %) with the oil from *Perilla ocimoides* (  $\alpha$ -linolenic acid: 56 wt %). And the natural vitamin mix (containing *d*- $\alpha$ -tocopherol at 50 wt %) was added to the oil at a ratio of 0.05 wt % for the oil.

After this mixture was preliminarily emulsified at 70°C for 15 min, the emulsified solution was obtained by a homogenous treatment using a two-stage homogenizing method with 200 kg/cm<sup>2</sup> for the first stage and 50 kg/cm<sup>2</sup> for the second stage, and then this emulsified solution was dried using a spray dryer to obtain the powdered product.

The powdered product obtained in this way was placed into a fluidized bed granulation machine and granulated with spraying purified water to the fluidized bed. Each of 15 g of this granulated product was tightly sealed in a small bag of

aluminium foil with nitrogen sealing. When 15 g of this granulated product in the small bag was dissolved in 150 ml of hot water and drunk, it could be drunk with nice taste without irritating and nasty flavors.

The granulated product in the small bag after storage for 6 months at room temperature had no problem since its color, smell and aspects were not changed as compared with those of the product just after the production, and since the peroxidation value (POV) of the oil component in the granulated product was as low as 5.0 meq/kg. Also this was drunk with nice taste by dissolving in hot water.

Moreover, this granulated product was dissolved in a commercially available concentrated liquid food (Sunate-A) and administered by transcatheter. When this dissolved solution was left at room temperature for 8 hours and at 5°C for 2 days, its emulsion stability was good without separation of the oil phase. Besides, in both cases, its POV was not increased.

Table 1.

Mixed materials	Mixed amounts (g)
EPA, DHA concentrated fish oil	20.0
Oil from <i>Perilla ocimoides</i>	12.0
Soy bean lecithin	8.0
Sodium casein	10.0
Enzymatic digestion product of lactalbumin	10.0
Powdered skimmed milk	20.0
Dextrin	18.0
Succinate monoglycerine	0.8
Fruit juice	1.0
Disodium phosphate	0.2

(Comparative example 1)

The granulated product was obtained and tightly sealed in the small bag as is the case with Example 1 except removal of lecithin in the mixed materials in Table 1 of Example 1. After this was stored at room temperature for 6 months, it could not be used as the product because a blinky smell was strong when its smell was evaluated.

(Example 2)

The materials at 100 parts by weight of mixed composition shown in Table 2 were added to water at 200 parts by weight and heated up to 70°C. Egg yolk lecithin and tetraglycerine pentaoleate were added after they were previously dissolved in the combined oil of the purified fish oil (EPA: 10 wt %, DHA: 8 wt %) with the oil from beefsteak plant seeds (  $\alpha$ -

linolenic acid: 63 wt %). And the natural vitamin mix was added the oil at a ratio of 0.05 wt % for the oil. After this mixture was preliminarily emulsified at 75°C for 15 min, the emulsified solution was obtained by a homogenous treatment using a two-stage homogenizing method with 200 kg/cm<sup>2</sup> for the first stage and 50 kg/cm<sup>2</sup> for the second stage, and then this emulsified solution was dried using a spray dryer to obtain the powdered product. Each of 1 kg of this powdered product was placed in a bag of aluminium foil with a deoxidizer (Ageless Z-20 made by Mitsubishi Gas Chemical Co. Ltd.), and stored at room temperature for 6 months, showing a good state without a degradation smell. When this product was used as a part of raw materials for pudding, margarine, spread, sausage, and ice cream, their flavors were good without nasty taste and smell of fish oils.

Table 2

Mixed materials	Mixed amounts (g)
Purified fish oil	35.0
Oil from beefsteak plant seeds	35.0
Egg yolk lecithin	3.0
Sodium casein	10.0
Enzymatic digestion product of soy beans	16.0
Tetraglycerine pentaoleate	0.3
Flavor	0.7

(Example 3)

The materials at 100 parts by weight of mixed composition

except lactalbumin and powdered skimmed milk shown in Table 3 were added to water at 200 parts by weight and heated up to 70°C. Citrate monoglyceride was added after it was previously dissolved in the combined oil of the concentrated fish oil containing EPA and DHA (EPA: 25 wt %, DHA: 14 wt %) with the oil from *Perilla ocimoides* (  $\alpha$ -linolenic acid: 58 wt %). And the natural vitamin mix was added the oil at a ratio of 0.05 wt % for the oil. After this mixture was preliminarily emulsified at 75°C for 15 min, the emulsified solution was obtained by a homogenous treatment using a two-stage homogenizing method with 150 kg/cm<sup>2</sup> for the first stage and 50 kg/cm<sup>2</sup> for the second stage, and then this emulsified solution was dried using a spray dryer to obtain the powdered product.

Lactalbumin and powdered skimmed milk shown in Table 3 were mixed with this powdered product in powder by powder. The powdered product obtained in this way was placed into a fluidized bed granulation machine and granulated with spraying purified water to the fluidized bed.

Each of 20 g of this granulated product was tightly sealed in a small bag of aluminium foil with nitrogen sealing.

When this granulated product in the small bag was added to hot water or orange juice, dissolved and drunk, it was drunk with nice taste without a fish oil smell and nasty taste. Also, the product was found to have no problem in quality without

generation of a degradation smell and nasty taste when it was examined after storage at room temperature for 6 months.

Table 3

Mixed materials	Mixed amounts (g)
Sodium casein	10.0
Enzymatic digestion product of casein	5.0
Lactalbumin	30.0
Powdered skimmed milk	13.7
EPA, DHA concentrated fish oil	10.0
Oil from <i>Perilla ocimoides</i>	10.0
Water soluble lecithin (enzymatic modified lecithin)	19.0
Citrate monoglyceride	1.0
Decaglycerine sesquistearate	0.3
Flavor	1.0

(Example 4)

The granulated product was obtained as is the case with Example 1 except a change of lactalbumin enzymatic digestion product to powdered skimmed milk in Example 1.

(Example 5)

The granulated product was obtained as is the case with Example 1 except a change of lactalbumin enzymatic digestion product to egg albumin enzymatic digestion product in Example 1.

Each product obtained from said examples and comparative example was left in a water bath at 30°C, and POV of the oil component included in each product was measured with time by a standard method, and showed in Table 4.



Table 4

	POV of oil component				
	Periods				
	0 month	1 month	2 months	3 months	4 months
Example 1	0.91	1.73	2.23	3.03	3.24
Example 2	0.74	0.27	0.46	1.18	1.43
Example 3	0.98	1.80	2.51	2.97	4.15
Example 4	1.29	2.61	2.84	6.24	8.01
Example 5	1.19	2.32	3.17	5.76	7.21
Comparative Example 1	3.21	34	82	120	202

From the above-mentioned results, it is obvious that the composition of the present invention is remarkably excellent in its oxidative stability.

[Advantage of the Invention]

The powdered composition for prevention of thrombus of the present invention has the characteristics shown as follows.

(1) It can be readily drunk with nice taste as a beverage by dissolving at the time of from 4 to 6 months passed after the production due to its excellent storage stability.

(2) It has pathological improving effects for diseases with arteriosclerosis, thrombosis, and cerebrovascular disorders and can be used as curative and preventive drugs for such diseases, as well as can be also used for the purposes of both nutritious maintenance and cure/prevention of diseases since it has effects of enhancement of physical capacity and of prevention of complications as it contains lots of proteins.

(3) It can be dissolved with easy stirring and drunk with nice taste because it is powdered and granulated, and remarkably good in solubility for water. Also, it can be readily dissolved in liquid concentrated liquid foods and juices, and is easy to be utilized.

(4) It can be used without oxidative degeneration of fats and oils when its solution is left for a long time (e.g., used as enteral nutrition) because its emulsified state after dissolution is good.

[Claim]

A powdered composition for prevention of thrombus characterized by containing (A) from 20 to 70 % of fats and oils containing 10 % or more eicosapentaenoic acid and docosahexaenoic acid and/or fats and oils containing 20 % or more  $\alpha$ -linoleic acid by weight, (B) from 2 to 20 % lecithin by weight and (C) from 20 to 70 % proteins and/or their degradation matters by weight.